

BENZODIAZEPINES (Systemic)

Lorazepam (parenteral only).

Anticonvulsant³%Clobazam; Clonazepam; Clorazepate; Diazepam; Lorazepam (parenteral only); Nitrazepam.

Antipanic agent³%Alprazolam; Chlordiazepoxide (parenteral only); Clonazepam; Diazepam; Lorazepam.

Skeletal muscle relaxant adjunct³%Diazepam; Lorazepam.

Antitremor agent³%Alprazolam; Chlordiazepoxide (oral only); Diazepam (oral only); Lorazepam (oral only).

Antiemetic, in cancer chemotherapy³%Lorazepam (parenteral only).

Indications

Note: Because ketazolam and prazepam are not commercially available in the U.S. or Canada, the bracketed information and the use of the superscript 1 in this monograph reflect the lack of labeled (approved) indications for these medications.

Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Anxiety (treatment)³%Alprazolam 3, 52, 59, bromazepam 60, chlordiazepoxide 41, clorazepate 19, diazepam 4, 24, 96, 113, halazepam 6, [ketazolam 63] *, lorazepam 7, 9, oxazepam 55, and [prazepam 56] * are indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Chlordiazepoxide 34, 41, [oral diazepam] *, and sublingual 9 or intramuscular lorazepam 9 are indicated for treatment of preoperative apprehension and anxiety.

Benzodiazepines are not indicated for the treatment of anxiety or tension associated with the stress of everyday life 3, 7, 24, 55, 60.

Effectiveness of these medications for long-term management of anxiety has not been assessed in systematic clinical studies 3, 7.

Alcohol withdrawal (treatment)³%Chlordiazepoxide 41, clorazepate 19, diazepam 4, 24, 113, [lorazepam] *, and oxazepam 55 are indicated for the relief of acute alcohol withdrawal symptoms such as acute agitation, tremor, impending or acute delirium tremens, and hallucinosis.

Anesthesia, adjunct³%Parenteral chlordiazepoxide 41 and parenteral diazepam 4, 24, 113 are indicated as premedication to relieve anxiety and tension in patients who are to undergo surgical procedures. Also, parenteral lorazepam is indicated in adults as preanesthetic medication to produce sedation, relief of anxiety, and anterograde amnesia 54.

Amnesia, in cardioversion or

Anxiety, in cardioversion (treatment) Parenteral diazepam is indicated for intravenous administration prior to cardioversion to relieve anxiety and tension and to produce anterograde amnesia 4, 24, 69, 113.

Amnesia, in endoscopic procedures or

Anxiety, in endoscopic procedures (treatment adjunct) Parenteral diazepam 4, 24, 69, 113 and [parenteral lorazepam] * are indicated as adjuncts prior to endoscopic procedures if apprehension, anxiety, or acute stress reactions are present and to diminish patient's recall of the procedure. Safety and efficacy have not been established for the use of diazepam prior to bronchoscopy or laryngoscopy 113.

[Sedation, conscious] * Parenteral diazepam is used in dentistry to relieve anxiety and produce amnesia in prolonged or difficult dental procedures. It is used frequently with a local anesthetic. 1

Molecular weight Alprazolam: 308.77 12

Mechanism of action/Effect:

In general, benzodiazepines act as depressants of the central nervous system (CNS) 8 , producing all levels of CNS depression from mild sedation to hypnosis to coma, depending on dose 2.

Although the precise mechanisms of action have not been completely established, it is believed that benzodiazepines enhance or facilitate the action of gamma-aminobutyric acid (GABA) 8, 18 , the major inhibitory neurotransmitter in the CNS 18, 38 , by causing it to bind more tightly to the GABA type A (GABA A) receptor 38.

Benzodiazepines reportedly act as agonists at the benzodiazepine receptors 8 , which have been shown to form a component of a functional 136, 139 supramolecular unit 133, 139 known as the benzodiazepine-GABA receptor-chloride ionophore complex. This receptor complex, which resides on neuronal membranes 135, 137 , functions mainly in the gating of the chloride channel 140.

Activation of the GABA receptor results in the opening of the chloride channel 133, 141, 142 , allowing the flow of chloride ions into the neuron 38.

Benzodiazepines reportedly increase the frequency of chloride channel opening 2, 8, 133.

There is also evidence that benzodiazepines may act at GABA-independent receptors 2.

Antianxiety agent; sedative-hypnotic Believed to stimulate GABA receptors in the ascending reticular activating system. Since GABA is inhibitory, receptor stimulation increases inhibition and blocks both cortical and limbic arousal following stimulation of the brain stem reticular formation. 156

Amnestic Mechanism of action has not been determined. However, as may occur with all sedative-hypnotic medications, preanesthetic doses of diazepam and lorazepam impair recent memory and

interfere with the establishment of the memory trace, thus producing anterograde amnesia for events occurring while therapeutic concentrations of the benzodiazepine are present. 2

Drug interactions and/or related problems:

Antacids may delay but not reduce the absorption of diazepam.

Premedication with diazepam may decrease dose of a fentanyl derivative required for induction of anesthesia and decrease time to loss of consciousness with induction doses.

Diazepam in parenteral dosage forms adheres to plastic infusion tubing.

Isoniazid may inhibit elimination of diazepam, resulting in increased plasma concentrations.

Rifampin may enhance elimination of diazepam, resulting in decreased plasma concentrations.

Medical considerations/contraindications:

Initiation or abrupt withdrawal of diazepam in patients with epilepsy or a history of seizures may precipitate seizures or status epilepticus. Use of intravenous diazepam for absence status or Lennox-Gastaut syndrome status may precipitate tonic status epilepticus.

Hypoalbuminemia may predispose patient to increased incidence of sedative side effects.